CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761164Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

Application Number(s)	761164
Associated IND	128190
Link to EDR	\\CDSESUB1\evsprod\BLA761164\
Submission Date	3/13/2020
Submission Type	Original BLA
Proposed Brand Name	Enjaymo
Generic Name	Sutimlimab
Pharmacologic Class	Monoclonal antibody
Dosage Form and Strength	Injection: 1100 mg/22 mL (50 mg/mL) as a clear solution in a single-dose vial
Route of Administration	Intravenous (IV) infusion
Proposed Indication	Treatment of hemolysis in adult patients with cold agglutinin disease (CAD)
Applicant	Bioverativ Therapeutics, Inc
OCP Review Team	Xiaolei Pan, Sudharshan Hariharan, Jihye Ahn, Justin Earp, Shirley Seo
OCP Final Signatory	Shirley Seo Director Division of Cardiometabolic and Endocrine Pharmacology (DCEP)

Contents

1. EXECUTIVE SUMMARY

This clinical pharmacology review is for an original BLA submitted by Bioverativ Therapeutics on March 13, 2020. The Applicant is seeking approval of Enjaymo, an IV injection of sutimlimab, for the treatment of hemolysis in adult patients with cold agglutinin disease (CAD). Sutimlimab is an immunoglobulin G (IgG), subclass 4 (IgG4) monoclonal antibody (mAb) that targets and inhibits the classical complement pathway (CP) and specifically binds to complement protein component 1, s subcomponent (C1s), a serine protease for C4. Inhibition of the classical complement pathway at the level of C1s prevents deposition of complement deposition on the surface of red blood cells, resulting in inhibition of hemolysis in patients with CAD. The proposed dosing regimen is 6.5 g or 7.5 g (based on body weight) administered intravenously. The dosing schedule consists of an initial dose (Day 0), followed by a dose one week later (Day 7), which is then followed by maintenance dose every other week beginning on Day 21.

The clinical development program includes three Phase 1 clinical pharmacology studies (i.e., single- and multiple-ascending dose evaluation, and a bridging study in Japanese subjects), and one Phase 3 efficacy/safety trial (CARDINAL). The Applicant is seeking approval of sutimlimab relying on the efficacy and safety findings from CARDINAL. The submission also includes one report for the development of population pharmacokinetic (PPK) models for sutimlimab, and one report for the development of an exposure-response relationship.

Key issues addressed in this review are:

(1) Appropriateness of the proposed dosing regimen for the indicated population

(2) Appropriateness of immunogenicity data to support labeling

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the information contained in BLA 761164 and determined that this BLA is approvable from a clinical pharmacology perspective.

	Sufficiently Supported?	**Comments**
Overall	☑ Yes ☐ No ☐ NA	Acceptable
General dosing instructions: 6.5 g (b) (4) or 7.5 g (BW ≥ 75 kg) as an IV infusion (over 1 to 2 hours) once per week for the first 2	☑ Yes ☐ No ☐ NA	The primary evidence of effectiveness comes from part A of the pivotal phase 3 trial (CARDINAL). The proposed dosing regimen is supported by a statistically significant and clinically

weeks, followed by every other week (Q2W)		meaningful improvement in responder rate, defined as patients who • did not receive blood transfusion from Week 5 to EOS • did not receive any other treatment for CAD • Hgb response was ≥12 g/dL, or increased by ≥2 g/dL from baseline at the treatment assessment endpoint
Dosing individualization in patient subgroups (intrinsic and extrinsic factors)	☑ Yes ☐ No ☐ NA	The recommended dose depends on the patient's body weight at baseline, since body weight is an important covariate on the exposure of sutimlimab: • 6.5 g (b) (4) • 7.5 g in patients ≥ 75 kg No other intrinsic or extrinsic factor requires dose individualization
Effect of immunogenicity on PK, efficacy, and safety	☑ Yes ☐ No ☐ NA	None of the 24 patients enrolled in the CARDINAL study who received at least one dose of sutimlimab developed treatment-emergent ADAs.
Labeling	☑ Yes ☐ No ☐ NA	Acceptable

1.2 Post-Marketing Requirements and Commitments

NA

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Summary of Clinical Pharmacology Findings

The Applicant has submitted three Phase 1 clinical pharmacology studies, with several subparts in each of these studies covering single-ascending dose PK/PD in healthy volunteers, multiple-ascending dose PK/PD in healthy volunteers, single-dose and multiple-dose PK/PD in healthy Japanese volunteers, and multiple dose study in patients with a complement-mediated disorder including renal allograft antibody mediated rejection (AMR), BP (bullous pempigoid), WAIHA (warm autoimmune hemolytic anemia), and CAD.

Population pharmacokinetic analysis was performed to evaluate the effect of intrinsic and extrinsic factors on sutimlimab pharmacokinetics. Summarized below are the key clinical pharmacology findings from the submitted studies:

Distribution

- Sutimlimab binds to C1s in the serum.
- The volume of distribution at steady-state is approximately 5.8 L in patients with CAD

Elimination

- Sutimlimab is a protein. It is generally recognized that antibodies are metabolized by degradation into small peptides and individual amino acids
- Sutimlimab clearance (CL) is governed by 2 parallel elimination pathways: a nonlinear, target mediated pathway predominating at low concentrations (20 - 100 μg/mL) and a nonspecific, linear pathway predominating at higher concentrations (>100 μg/mL).
- Linear CL is predominant over the range of plasma concentrations achieved at the proposed dosing regimen. The population PK model predicted linear CL of sutimlimab is 5.65 mL/h (~0.14 L/day).
- The distribution and terminal elimination half-lives ($t_{1/2\alpha}$ and $t_{1/2\beta}$, respectively) of sutimlimab are 0.84 and 20.9 days, respectively, at the recommended dose.

Intrinsic Factors

- Sex, age and race: No clinically significant differences in the pharmacokinetics of sutimlimab were observed based on sex, age (19 to 88 years old), or ethnicity (Japanese, non-Japanese).
- Body weight: Population pharmacokinetic analysis showed that sutimlimab exposures decreased up to 59% for a subject weighing 98 kg, and increased up to 57% for a subject weighing 50 kg as compared with a patient weighing approximately 72 kg. The effect of body weight on pharmacokinetics has been integrated in the recommended dose regimen tiered by body weight.
- Hepatic impairment: The effects of hepatic impairment on the pharmacokinetics of sutimlimab is unknown (no dedicated study was performed, and no population PK analysis was conducted).
- Renal impairment: Based on the population PK report, no clinically significant differences in the pharmacokinetics of sutimlimab were observed for patients with mild to moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m^2). The effect of severe renal impairment on the pharmacokinetics of sutimlimab is unknown.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended dose is 6.5 g for patients (b) (4) and 7.5 g for patients weighing 75 kg or more. Administer sutimlimab intravenously weekly for the first two weeks, with administration every other week thereafter.

If a dose is missed, administer as soon as possible; thereafter, resume dosing every two weeks. If the duration after the last dose exceeds 17 days, restart dosing weekly for two weeks followed by every two-week dosing.

2.2.2 Therapeutic individualization

Body Weight: The recommended dosage of sutimlimab for patients with CAD is based on body weight. Refer to general dosing (2.2.1) for details.

2.3 Outstanding Issues

NA

2.4 Summary of Labeling Recommendations

The review team addressed the following issues in the package insert:

- (b) (4) the review team requested anti-drug antibody (ADA) data from CARDINAL using a modified ADA assay. With the modified assay which was deemed acceptable by OBP, the results showed that none of the 24 patients enrolled in CARDINAL who received at least one dose of sutimlimab developed treatment-emergent ADAs. The language in Section 6.2 Immunogenicity was updated accordingly.
- The language in Section 12 Clinical Pharmacology of the label were revised according to the FDA Guidance for Industry - Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Sutimlimab is a first-in-class, humanized IgG4 mAb that targets the classical complement pathway (CP) by inhibiting the CP-specific serine protease, C1s. Sutimlimab is developed as a sterile IV infusion formulation containing sutimlimab 50 mg/mL for the treatment of hemolysis in adult patients with CAD,

a complement-mediated life-threatening disease. Inhibition of the classical complement pathway at the level of C1s prevents deposition of complement opsonins on the surface of red blood cells, resulting in inhibition of hemolysis in patients with CAD.

The development of sutimlimab (under IND 128190) for the treatment of CAD was granted orphan drug designation on July 2016 and breakthrough therapy designation in May 2017. The Applicant submitted the BLA on March 13, 2020. The evidence in support of sutimlimab's efficacy and safety for CAD is derived primarily from a pivotal Phase 3 trial – an open-label Study 03 (CARDINAL) in CAD patients with Hgb levels ≤10.0 g/dL and a recent history of blood transfusion. A double-blind, placebo controlled, Phase 3 study, CADENZA, in symptomatic patients with CAD who have Hgb levels ≤ 10.0 g/dL and who do not have a recent history of blood transfusion is currently on-going. The CADENZA study report will be submitted post-marketing.

3.2 General Pharmacological and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of action	Sutimlimab is an IgG4 mAb that inhibits the CP pathway and specifically binds to C1s, a serine protease which cleaves C4. Inhibition of the classical complement pathway at the level of C1s prevents deposition of complement opsonins on the surface of red blood cells, resulting in inhibition of hemolysis in patients with CAD.
QT prolongation	Large targeted proteins and monoclonal antibodies have a low likelihood of direct ion channel interactions. A thorough QT/QTc study is not necessary, unless the potential for proarrhythmic risk is suggested by mechanistic considerations or data from clinical or nonclinical studies.
General Information	
Bioanalysis	PK Two validated enzyme-linked immunosorbent assays (ELISA) were developed to measure the concentrations of sutimlimab in serum samples collected from both patients and healthy subjects in the clinical studies included in this BLA. PD Semi-quantitative ELISA assays were developed to measure the PD response for sutimlimab, including CP and alternative pathway (AP) activity, PD biomarkers (C1q, C1s, CH50, C1sC1INH) concentrations, in the serum samples collected from both patients and healthy subjects. A validated quantitative LC-MS/MS method was

	developed to measure total C1s concentration in plasma sampled collected from patients in CARDINAL. <u>Immunogenicity</u> Three assays were developed to detect antidrug antibodies (ADAs) directed against sutimlimab. However, only two of the methods were validated with different reported sensitivity and drug tolerance.	
Healthy volunteers vs. patients	PK was similar between CAD patients and healthy subjects	
Drug exposure at steady-state following the therapeutic dosing regimen	Based on the population PK analysis, the means (SD) of C_{min}, C_{max} and AUC_{tau} at steady-state were 1516 (913) µg/mL, 3447 (1216) µg/mL, and 734627 (335279) µg*hr/mL, respectively.	
Effective dose or exposure	The IC_{90} of sutimlimab for CP inhibition in vitro was ~ 63.9 µg/mL. In clinical trials, CP activity was consistently inhibited at concentrations above 100 µg/mL.	
Maximum tolerated dose or exposure	Single dose	100 mg/kg sutimlimab was the highest dose tested; and a maximum tolerated dose (MTD) was not identified.
	Multiple dose	75 mg/kg sutimlimab was the highest dose tested.
Dose proportionality	The mean $AUC_{0-\infty}$ increased in a greater than dose-proportional manner over the 3 to 30 mg/kg dose range, but increased in an approximately dose-proportional manner over the 60 to 100 mg/kg dose range (0.3 to 1.5 times the maximum approved recommended dosage based on 75 kg).	
Variability	The variability in steady-state C_{trough} in CAD patients at the recommended dose regimen ranged from 39.6% to 78.6%. The inter-individual variability for linear CL and central volume of distribution was estimated as 34% and 21%, respectively, based on population PK analysis.	
Accumulation	Steady-state appears to be achieved by Week 7. The accumulation ratios were determined to be 1.8 for AUC_{0-168h} and 1.5 for C_{max} following 75 mg/kg of sutimlimab doses on Days 1, 8, 22 and 36.	
Immunogenicity	• In part A of CARDINAL, none of the 24 patients enrolled who received at least one dose of sutimlimab developed treatment-emergent ADAs. • In healthy subjects, 13% (4 out of 30 subjects) had confirmed ADAs on end of study (EOS) days.	

Absorption	
T_{max}	Immediately following IV infusion
Absolute bioavailability	Not applicable (N/A) as sutimlimab is administered intravenously
Distribution	
V_d	5.8 L
Protein binding	N/A
Substrate of transporter systems	N/A
Elimination	
$T_{1/2}$	The terminal elimination half-life is 21 days
Primary elimination pathways	Catabolism in plasma
Metabolism	
Primary metabolizing enzymes	Metabolized by degradation into small peptides and individual amino acids
Inhibitor/Inducer	N/A

3.3 Clinical Pharmacology Questions

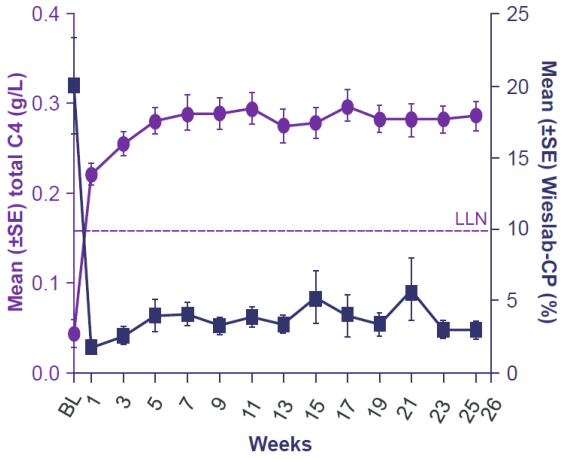
3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The primary evidence of effectiveness of sutimlimab is based on results from the pivotal trial, CARDINAL, which is discussed later in this section. From a clinical pharmacology perspective, supportive evidence of effectiveness comes from the effect of sutimlimab on markers such as C4 and bilirubin that are indicative of classical pathway (CP) inhibition and the exposure-CP inhibition relationship.

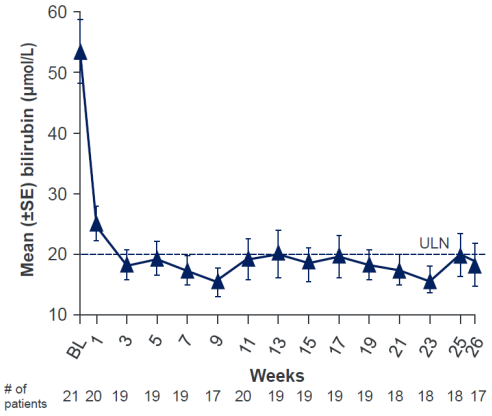
Sutimlimab is an antibody that is directed against human complement factor C1s, which along with C1r and C1q is a part of the C1 complex that sits at the apex of the CP. Based on its proposed mechanism of action, by binding C1s, sutimlimab prevents the enzymatic action of the C1 complex on its substrate C4, and thereby blocks the formation of the C3 convertase; while other complement pathways remained functionally intact.

In CARDINAL, greater than 90% inhibition of CP was observed following a single sutimlimab infusion and sustained in patients with CAD when sutimlimab concentrations were greater than or equal to 100 µg/mL (Figure 1 (a)). C4 levels returned to normal levels (0.2 g/L) in patients with CAD within one week following the first dose of sutimlimab (Figure 1 (a)). Complete CP inhibition following initiation of sutimlimab treatment led to inhibition of hemolysis as evidenced by normalization of bilirubin (Figure 1 (b)). After the first treatment with sutimlimab, near normalization of bilirubin associated with a greater than 1 g/dL increase in hemoglobin was observed, demonstrating the effect on CP inhibition (Figure 1 (c)). The extent and duration of the pharmacodynamic response in patients with CAD were exposure dependent for sutimlimab. This result provides supportive evidence for sutimlimab for its mechanism of action.

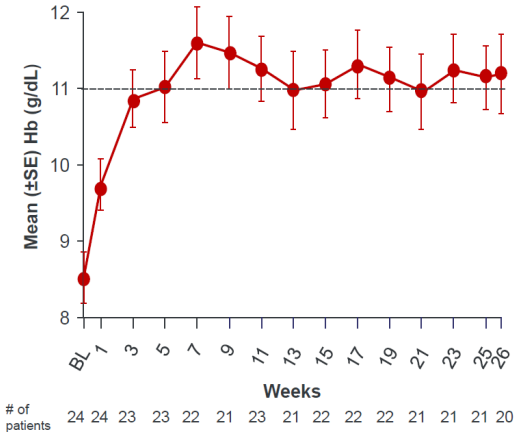
Figure 1. The changes of PD parameters following sutimlimab administration in CARDINAL



(a)



(b)



(c)

Based on PK/PD analysis, a concentration-effect relationship was observed for the inhibition of serum CP activity. Based on the inhibitory maximal effect (E_{max}) model, the maximum percent inhibition (I_{max}) of sutimlimab on CP activity was 90.9%, with a concentration for half-maximal effect (IC_{50}) of 7.1 µg/mL and IC_{90} of 63.9 µg/mL. Sutimlimab demonstrates rapid clearance due to target mediated drug disposition (TMDD) observed at concentrations <100 µg/mL. In order to maintain a near-maximal inhibition of CP activity and to avoid nonlinearity in PK, 100 µg/mL was chosen as an appropriate target concentration for sutimlimab dose selection.

The primary evidence of effectiveness is from the pivotal trial, CARDINAL, which was an open label, multicenter, single arm study in CAD patients who have a recent history of blood transfusion. Patients (N = 24) received sutimlimab IV at either 6.5 g (if < 75 kg) or 7.5 g (if ≥ 75 kg) doses based on their baseline body weight on Days 0 and 7, and biweekly thereafter. Patients had an end of treatment (EOT) visit on Day 182 (Week 26). Given that this was a single arm study in patients with a high unmet medical need, stringent criteria consistent with amelioration of hemolytic anemia that is responsible for the clinical presentation of this severe condition, were set for the primary endpoint of responder rate as defined by:

- Patients who did not receive a blood transfusion from Week 5 through Week 26 (EOT)
- Patients who did not receive treatment for CAD beyond what was permitted per protocol
- Patients with hemoglobin level:
  - ≥12 g/dL at the treatment assessment endpoint, or
  - increased by ≥2 g/dL from baseline at the treatment assessment endpoint.

A total of 13 patients (54.2%, 95% CI: 32.8 to 74.4) were responders for sutimlimab treatment. This result met the predefined statistical criteria for primary endpoint of lower bound of the 95% CI >30%. Moreover, 6 of the 11 patients who did not meet the criteria for the primary endpoint did achieve important clinically meaningful improvement in their disease as measured by normalization of bilirubin levels, improvement in hemoglobin levels, and improvement in functional assessment of chronic illness

therapy (FACIT)-Fatigue scale scores at the treatment assessment endpoint. Additional details supporting efficacy of sutimlimab can be found in the clinical and statistical reviews by Drs. Carrie Diamond and Yaping Wang).

3.3.2 Is the proposed general dosing regimen appropriate?

The proposed dosing regimen is appropriate. The proposed dosing regimen is supported by favorable efficacy and safety results from CARDINAL, the population pharmacokinetic analyses using 4 clinical studies (Studies 01, 02, CARDINAL, and 05), and the exposure-response (E-R) analysis in CAD patients from CARDINAL.

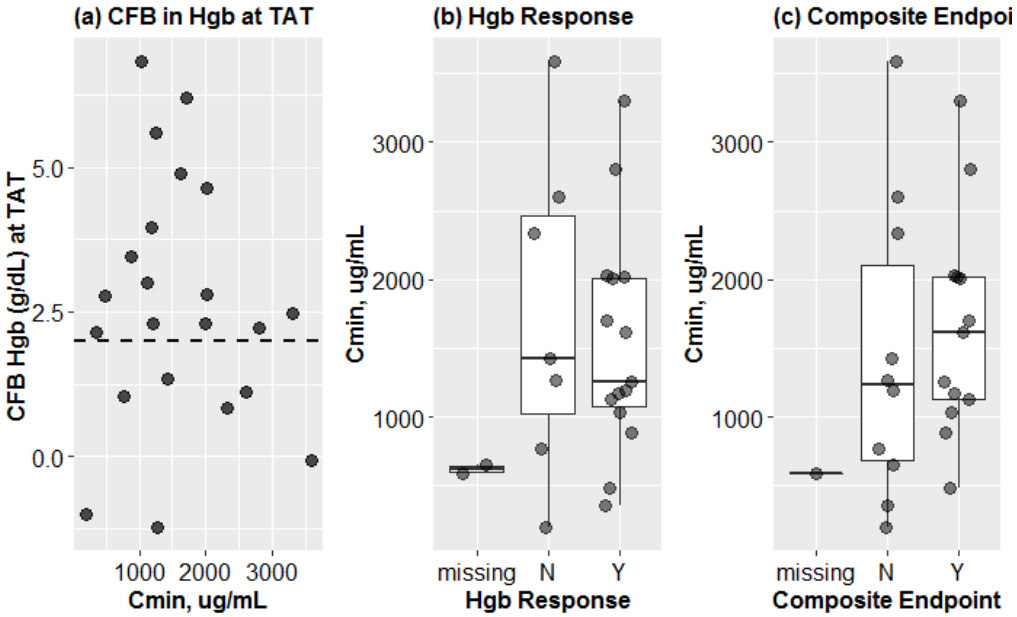
The proposed dosing regimen was studied in CARDINAL. The Applicant selected this dosing regimen for the Phase 3 program based on the population PK analysis (Study No. TNTH-CSC-103) developed using Phase 1 data. The main consideration in selecting the dosing regimen was to maintain sutimlimab trough concentrations above the concentration target of 100 μg/mL in all CAD patients to avoid breakthrough hemolysis. The Applicant's analysis included the simulations of a flat dose (5.5 g), a body weight-based dosing regimen (75 mg/kg) and a two-tiered flat dosing (6.5 g in subjects <75 kg and 7.5 g in subjects ≥75 kg). The body weight-based dosing (i.e., 75 mg/kg) was expected to markedly reduce the variability in trough concentrations across the body weight range; however, the proportion of subjects with trough concentrations below the concentration target was expected to be substantially greater in the lower body weight groups. With one flat dose (i.e., 5.5 g), the proportion of subjects with trough concentrations below the concentration target was expected to be greater in the higher body weight groups. With the two-tiered flat dosing (6.5 g in subjects <75 kg and 7.5 g in subjects ≥75 kg), overall, only 6.2% of subjects were expected to have trough concentrations below 100 μg/mL and the proportion of subjects with trough concentration below the target was generally similar across the body weight range. In CARDINAL where the two-tiered flat dosing was administered, only two patients (8.3%) had sutimlimab concentrations lower than 100 μg/mL throughout the 26-week treatment period.

Furthermore, the E-R relationship in CAD patients from CARDINAL was evaluated for the following efficacy variables: a) hemoglobin change from baseline at treatment assessment time (TAT, defined as the average of the values from Week 23, 25, and 26 visits), b) hemoglobin response defined by either Hgb ≥ 12 g/dL or increase ≥ 2 g/dL from baseline, and c) the primary efficacy endpoint for CARDINAL which was defined by hemoglobin response AND patients not receiving transfusion during Week 5 to Week 26. Exposure metric used in E-R analysis is trough concentrations (C_{min}) at steady-state estimated with the population PK model.

The E-R analysis did not reveal any notable relationship between C_{min} and hemoglobin response in the estimated range of C_{min} (197.5 - 3584 μg/mL) in the patients from CARDINAL. There is no trend between C_{min} values and the change from baseline at TAT in hemoglobin levels (Figure 2 (a)). C_{min} levels largely overlapped between responders and non-responders for hemoglobin response (Figure 2 (b)) and the composite endpoint (Figure 2 (c)). As a clear E-R relationship is not evident in the estimated C_{min} range and all patients in CARDINAL have the estimated steady-state C_{min} above 100 μg/mL, the review team

concludes that the proposed dosing regimen provides an adequate exposure to achieve hemoglobin response in CAD patients.

Figure 2. Exposure-Response Relationship in CARDINAL Study (n=24)



Source: Reviewer's analysis. CFB: change from baseline. Hgb: hemoglobin. N=non-responders. Y=responders. Dashed line represents hemoglobin level increase by 2 g/dL from baseline to TAT.

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

The proposed dosing regimen is a two-tier weight-based dosing accounting for the impact of body weight on sutimlimab PK. No dose adjustment is needed based on other intrinsic factors such as ethnicity (Japanese and non-Japanese), and sex. Assessment of the magnitude of covariate effect on PK was evaluated using population PK analysis.

Body weight:

Population PK analysis identified patient's body weight as a significant covariate for sutimlimab PK. The dose normalized exposures are expected to vary from 157% to 41% for the body weight of 50.5 kg (5^{th} percentile) and 98 kg (95^{th} percentiles) relative to the median body weight of 71.9 kg. The two-tier weight-based dosing did not provide notable improvement in the variability of sutimlimab exposure (157% to 47% for the body weight of 50.5 kg and 98 kg). However, as the population PK analysis predicted (Refer to Section 3.3.2), the two-tier dose based on body weight are expected to increase the proportion of patients achieving trough concentrations above the 100 ug/mL) compared to the one flat dose (i.e., 6.5 g). In CARDINAL, the proposed weight-based dosing regimen was administered to

patients with body weights ranging from 40.2 kg to 112 kg, and the steady-state C_{min} and C_{max} decreased with increasing body weight and the estimated steady-state C_{min} was greater than 100 ug/mL for all patients (Figure 3).

Figure 3. Steady-state C_{min} by weight and ethnicity in patients from CARDINAL (n=24)

Source: Reviewer's analysis. Triangles/circles represents Japanese and non-Japanese, respectively. Red/blue dots represent female and male patients, respectively. Dashed line represents the PK target (100 ug/mL)

Ethnicity:

Ethnicity (Japanese vs. Non-Japanese) was identified as a significant covariate in population PK analysis. Sutimlimab exposures are estimated to be greater by 23% to 33% in Japanese compared to non-Japanese subjects. In CARDINAL, three Japanese patients received the proposed dosing regimen (triangles in **Figure 3**). Based on the lack of E-R relationship and the safety experience with the proposed dose regimen (two of Japanese patients had the highest exposures observed in CARDINAL), no dose adjustment is warranted based on ethnicity (Japanese and non-Japanese).

Sex:

Sex was not a significant covariate in population PK analysis. However, it was observed that the responder rate for the primary efficacy endpoint in male patients (22%) was notably lower than that in female patients (73%) (Refer to Section 4.2 Pharmacometrics Review for further details). The difference in efficacy between female and male patients is not likely due to the PK difference between male and female patients, hence, no dose adjustment is needed based on sex.

Renal Impairment

No dedicated study was conducted in subjects with renal impairment. Population PK analysis revealed that there is no clinically significant change in sutimlimab clearance in patients with mild to moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m^2). There were no sufficient data to evaluate the influence of severe renal impairment on sutimlimab PK.

Hepatic impairment

No dedicated study was conducted in subjects with hepatic impairment.

3.3.4 What is the immunogenicity profile of sutimlimab?

- Healthy subjects

Immunogenicity was assessed using method TN-1623 for Study 01 (parts A-B) and method TN-1707 for Study 02 and Study 05 (part B).

Drug tolerance was not evaluated in Method TN-1623. In addition, method validation results indicate the approach to determine the screening cut point (SCP) and confirmatory cut point (CCP) are not appropriate, and this method showed a high false positive rate. Therefore, the ADA measurements using assay TN-1623 (e.g., Study 01 parts A – C) were not reliable and interpretable. For method TN-1707, the drug tolerance was determined to be 50 µg/mL at the sensitivity level of 100 ng/mL, indicating that ADA incidence results were not reliable unless the drug level in the sample was below 50 µg/mL. Additional details regarding the validation of immunogenicity assay can be found in the OBP review by Dr. Xiaoshi Wang.

Based on ADA sampling scheme and reported individual PK exposure at these ADA sampling times, all samples in Studies 02 and 05 (part B) except those collected at end of study (EOS) had drug levels greater than 50 µg/mL, indicating that only the ADAs samples at EOS were interpretable. Based on the ADA results measured at EOS, a total of 4 subjects (out of 30, 13%) had confirmed ADAs in Studies 02 and 05.

- CAD patients

Immunogenicity was assessed in Study 01 (part C) in patients with CAD using method TN-1623. However, due to deficiencies of the assay, the ADA data from Study 01 (part C) were not reliable and interpretable.

A recommendation (June 23, 2020) was sent to the Applicant for completing immunogenicity assay development and submitting a full validation report of the newly developed immunogenicity assay to detect ADA formation in patients enrolled in the pivotal clinical study CARDINAL. A new ADA assay validation report (Study ABV0020) was submitted on July 2, 2020 (eCTD 0014). The sensitivity was 75-100 ng/mL in the presence of 5 mg/mL sutimlimab, which met the general requirement for ADA detection for clinical studies and was determined to be suitable for use in the pivotal studies. Based on

the results submitted from CARDINAL Part A, none of the 24 patients enrolled in CARDINAL (who received at least one dose of sutimlimab) developed treatment-emergent ADAs, and thus the Applicant concluded there is no further need for Nab assay. The effect of immunogenicity on PK, efficacy, and safety of sutimlimab in patients cannot be assessed.

The review team concluded that the immunogenicity results from CARDINAL can be used to support labeling in Section 6.2 Immunogenicity. Considering the limited number of subjects (N = 24) and ADA samples in CARDINAL, it is recommended that the Applicant continue assessing the immunogenicity of sutimlimab, as planned, in the on-going study CADENZA.

3.3.5 Are the assays for PK and PD assessment adequate?

The FDA evaluated the applicant's bioanalytical methods for sutimlimab PK and PD assessments. The results are summarized in (Table 1). In summary, the assays for PK and PD assessments are adequate to support the approval of this BLA from a clinical pharmacology perspective. See details in Appendix Section 4.1 Summary of Bioanalytical Method Validation and Performance.

Table 1. Evaluation summary on the Applicant's bioanalytical methods

	Analyte	**Study Number**	**Method Validation**	**In Study Method Performance**
PK	Sutimlimab	TN-1608/1609	Acceptable	Acceptable
	Sutimlimab	TN-1702	Acceptable	Acceptable
PD	CP activity	TN-1610/1611	Semi-quantitative method	N/A
	CP activity	TN-1705	Semi-quantitative method	N/A
	AP activity	TN-1706	Semi-quantitative method	N/A
	C1s	LCMSD 954	Acceptable	Acceptable
	C4	C4	Acceptable	Acceptable
Immunogenicity	ADA	TN-1623	Not acceptable	Not acceptable
	ADA	TN-1707	Acceptable	Acceptable
	ADA	ABV0020	Acceptable	Acceptable

3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

Yes, the to-be-marketed formulation is the same as the clinical trial formulation.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

4.1.1 How are the active moieties identified and measured in the clinical pharmacology and biopharmaceutics studies?

Pharmacokinetic Measurement of Sutimlimab in Serum

Table 2. Summary of bioanalytical method measuring sutimlimab in serum

Bioanalytical method review summary	Method was adequately validated to support clinical studies		
Method 1608/1609			
Method description	An ELISA based bioanalytical method for the determination of the concentrations of functional sutimlimab (i.e., sutimlimab with 1 or both binding sites available to interact with the target, C1s) in human serum. This method was applied in clinical study 01 (Part A-C)		
Material for calibration curve & concentration	Sutimlimab (TNT009)		
Specificity/Interference	IgG4 spiked samples did not interfere in the recovery of sutimlimab		
Validated assay range	5 to 133 ng/mL		Acceptable
Selectivity	Selectivity data indicated no marked matrix effects		
Standard curve performance: accuracy and precision	Linearity	Accuracy: 93% to 114% Precision: ≤ 15% except 1 sample (STD7) at 19%	Acceptable (> 75% of non-zero standards meet the criteria including LLOQ)
LLOQ	5 ng/mL		
QC concentrations	5, 12.5, 50, 75, 133 ng/mL		
QCs performance during accuracy & precision	Intra-run accuracy (% bias)	QC high2: 123% QC high: 100% QC medium: 104% QC low: 103% QC low2: 102%	Acceptable
	Intra-run precision (%CV)	QC high2: 13 % QC high: 9 % QC medium: 9 % QC low: 7 % QC low2: 12 %	Acceptable

	Inter-run accuracy (%bias)	QC high2: 115% QC high: 96% QC medium: 97% QC low: 102% QC low2: 90%	Acceptable
	Inter-run Precision (%CV)	QC high2: 22 % QC high: 12 % QC medium: 11 % QC low: 8 % QC low2: 15 %	Acceptable
Bench-top stability	1 hour		
Freeze-Thaw stability	Up to 4 cycles at -60°C to -80°C		
Incurred sample re-analysis (ISR)	Pass Rate: 84%		Acceptable
Method 1702			
Method description	An ELISA based bioanalytical method for the determination of the concentrations of functional sutimlimab (i.e., sutimlimab with 1 or both binding sites available to interact with the target, C1s) in human serum. This method was applied in clinical Study 02, 03 and 05		
Material for calibration curve & concentration	Sutimlimab (TNT009)		
Specificity/Interference	IgG4 spiked samples did not interfere in the recovery of TNT009 at both low (40,000 ng/mL) and high (200,000 ng/mL) levels.		
Validated assay range	3.000 (LLOQ) to 200.000 (ULOQ) ng/mL		Acceptable
Minimum required dilution	1 in 2000		
Calibration model & Weighting factor	4 Parametric with no weighting		
Selectivity	Selectivity data indicated no marked matrix effects		
Standard curve performance: accuracy and precision	Linearity	Accuracy: (%Bias): -10.8% to 2.7% Precision (CV%) $\leqslant$ 9.4%	Acceptable
LLOQ	3 ng/mL		
QC concentrations	5, 12.5, 50, 100, 133 ng/mL		

QCs performance during accuracy & precision	Intra-run accuracy (% bias)	LLOQ: -15.1% to 18.0% LQC: -11.7% to 14% MQC: -15.1% to 1.8% HQC: -15.8% to 0.2% ULOQ: -10% to 10.6%	Acceptable
	Intra-run precision (%CV)	LLOQ: 1.8 to 4.3 % LQC: 1.6 to 6.5% MQC: 2.4 to 4.5% HQC: 4.5 to 5.7% ULOQ: 1.7 to 4.1%	Acceptable
	Inter-run accuracy (% bias)	LLOQ: 2.4% LQC: 3.9% MQC: -6.5% HQC: -6.8% ULOQ: 2.5%	Acceptable
	Inter-run Precision (%CV)	LLOQ: 7.6 % LQC: 9.3% MQC: 7.9% HQC: 9.1% ULOQ: 8.7%	Acceptable
Long term stability	Up to 20 months (585 days) at -60°C to -80°C		Acceptable
Bench-top stability	4 hour 16 minutes		Acceptable
Freeze-Thaw stability	Up to 7 cycles at -60°C to -80°C		Acceptable
ISR	Study 02: Pass rate 79.4%		Acceptable
	Study 03: Pass rate 87.7%		Acceptable
	Study 05: Pass rate 78.2%		Acceptable

Reviewer's comments:

- *Method 1608/1609 and Method 1702: Adequate to support the PK analysis for samples from Studies 01, 02, 03 and 05.*

Pharmacodynamic Measurement of Sutimlimab in Serum

A commercially available ELISA assay kit for the semi-quantitative measurement of CP activity was validated at (b) (4) (Method TN-1601/1611) for Study 01 (Parts A-C), and (b) (4) (Method TN-1705) for studies 02, 05, 01 Part E, and 03. The assay combines principles of the hemolytic assay for complement activation with the use of labeled antibodies specific for Membrane Attack Complex (MAC) produced as a result of classical complement activation. The amount of MAC generated is proportional to the functional activity of the classical complement pathway.

Table 3. Bioanalytical method performance summary: PD assays for sutimlimab in serum

Method TN-1610/1611		
Method description	Method TN-1610/1611 is an ELISA method for semi-quantitation of CP activity in complement preserved human serum. The assay consists of a microtiter plate coated with IgM which is capable of activating the endogenous CP, while the remaining complement pathways are blocked. Complement preserved human serum was diluted and added to the plate, the pathway was activated and C5b-9 was generated and bound to the plate. A C5b-9 specific alkaline phosphatase-conjugated antibody was used to detect bound C5b-9. Alkaline phosphatase was then added to achieve a signal intensity proportional to the concentration of plate bound-C5b-9. Classical complement pathway activity was calculated based on a standardized positive and negative control. An additional sutimlimab control was added to the method. The implementation of the control at 99 µg/mL sutimlimab in pooled human serum (TNT control) was considered reasonable as the control mimicked the expected study samples and was additionally used to demonstrate sample stability. The unspiked pooled serum was used to demonstrate the endogenous complement activity during validation and was not implemented into the method SOP. Method TN-1610/1611 was used for CP activity analysis for Study 01 (Parts A to C).	
Materials used for inhibition	0.2 µg/mL – 99 µg/mL sutimlimab	
Inhibition curve & concentration	No calibration curve; readout is % activity relative to a positive and negative control (5% to 99% complement activity)	
Regression model & weighting	N/A	
Calibration curve performance	N/A	
Range of classical complement pathway activity of healthy donors	80 % - 121 % complement activity from 30 individual serum samples	
Minimum required dilutions	1 in 101	
Validation parameters	Method validation summary	Acceptability
Accuracy and precision	Inter-assay and intra-assay precision were met for positive control: background subtracted optical density (blOD) of assay positive control >1.0, %CV was 1.7% - 2.7% (intra-assay) and 11.3% (inter-assay)	Acceptable
	Inter-assay and intra-assay precision was met for negative control: optical density of assay negative control <0.2	

	Inter-assay and intra-assay precision was met for pooled human serum: %Activity for pooled human serum control ≤ 10%	
Interference & Specificity	This assay was found to be specific as it can differentiate positive and negative controls, heat inactivated positive controls and sutimlimab spiked controls	
Benchtop/ process stability	4 hours	
Freeze-Thaw stability	3 cycles at -60°C to -80°C and thawed on ice	
Refrigerator stability	72 hours	
Method TN-1705		
Method description	Method 1705 is an ELISA method for semi-quantitation of CP activity in complement preserved human serum. The assay consisted of a microtiter plate coated with IgM, which is capable of activating the endogenous CP while the remaining complement pathways are blocked. Complement preserved human serum was diluted and added to the plate, the pathway was activated and C5b-9 was generated and bound to the plate. A C5b-9 specific alkaline phosphatase conjugated antibody was used to detect bound C5b-9. Alkaline phosphatase was then added to achieve a signal intensity proportional to the concentration of plate bound C5b-9. Classical complement pathway % activity was calculated based on a standardized positive and negative control. Method TN-1705 was used for CP activity analysis for Studies TNT009-02, BIVV009-05, BIVV009-01 (Part E*), and BIVV009-03	
Materials used for inhibition curve & concentration	No calibration curve; readout is % activity relative to a positive and negative control	
Regression model & weighting	N/A	
Calibration curve Performance	N/A	
Minimum required dilutions	1 in 1000	
Validation parameters	Method validation summary	Acceptability
QC levels	Positive control: 2.159 Blank Mean Optical Density (blOD) Negative control: 0.116 Optical Density (OD) TNT Control: 1.5%	
Accuracy and Precision	Accuracy (%bias) in 5 QCs: N/A	Acceptable

	Inter-Assay and Intra-Assay Precision was met for positive control: blOD of Assay positive control >1.0 (36 out of 36 replicate pairs from 6 runs met this criteria), %CV was 1.3% - 3.2% (Intra-Assay) and 4.1% (Inter- Assay)	
	Inter-Assay and Intra-Assay Precision was met for NC: OD of Assay NC <0.200 (36 out of 36 replicate pairs from 6 runs met this criteria), %CV was 1.2% - 25.8% (Intra-Assay) and 16.6% (Inter-Assay)	
	Inter-Assay and Intra-Assay Precision was met for pooled human serum control: %Activity for TNT control ⩽10% (34 out of 36 replicate pairs from 6 runs met this criteria), %CV was 2.1% - 36.6% (Intra-Assay) and 22.9% (Inter-Assay)	
Interference & Specificity	This assay was found to be specific as it can differentiate sutimlimab from a similar human IgG4 at the same concentration level (100 μg/mL)	
Benchtop/ process stability	23 hours 24 minutes	
Freeze-Thaw stability	6 cycles at -60°C to -80°C and thawed on ice	
Refrigerator Stability	20 months (619 days) months at -60°C to -80°C	
Selectivity & matrix effect	11 of 11 lots of normal serum passed all acceptance criteria. 4/6 CAD patient serum passed all acceptance criteria. It was expected that CAD patient serum would not all pass acceptance as the disease may cause depletion of classical complement pathway components.	
Hemolysis effect	Six lots of hemolyzed samples were tested. No matrix interference was observed in the %CP activity regardless of health status.	
Lipemic effect	Six lots of lipemic samples were tested. No matrix interference was observed in the %CP activity regardless of health status.	
Assay performance (Study 03)		
Materials used for calibration curve & QC	Wieslab Complement System Classical Pathway, Lot US 2207 (08Aug 2018) Wieslab Complement System Classical Pathway, Lot US 2928(02Aug 2019) Test article BIVV009, Lot # 0000434249 (Retest Date 24 June 2020)	
Assay passing rate	26 of 26 assays passed acceptance criteria. 697 of 699 samples had reportable results.	
Standard curve performance	N/A assay does not use a standard curve	
QC performance	• Assay positive control cumulative precision: 6.9 % CV • Assay negative control cumulative precision: 4.4 % CV • TNT Control Cumulative precision: 26.5 % CV	

Study sample analysis/ Stability	Long term stability is currently established up to 619 days at -60 to -80°C. All samples tested in this assay were analyzed within established stability.

Reviewer's comments: Methods 1610/1611 and 1705 are semi-quantitative for measuring CP activity in complement preserved human serum. %CP activity was calculated as activity relative to a positive and negative control.

Alternative complement (AP) functional activity

Method TN- 1706		
Method description	Method 1706 is an ELISA method for semi-quantitation of AP activity in complement preserved human serum. The assay consisted of a microtiter plate coated with lipopolysaccharide, which was capable of activating the AP while the remaining complement pathways were blocked. Complement preserved human serum was diluted and added to the plate, the pathway was activated and C5b-9 was generated and bound to the plate. A C5b-9 specific alkaline phosphatase conjugated antibody was used to detect bound C5b-9. Alkaline phosphatase was then added and signal intensity proportional to the concentration of plate bound C5b-9 was achieved. Alternative complement pathway activity was calculated based on a standardized positive (pooled complement preserved serum representing 100% activity) and negative control (heat treated pooled complement preserved serum representing full inhibition of activity). Method TN-1706 was used for AP activity analysis in Study 02	
Materials used for inhibition curve & concentration	No calibration curve; readout is % activity relative to a positive and negative control	
Regression model & weighting	N/A	
Calibration curve performance	N/A	
Minimum Required Dilution	1 in 18	
Validation parameters	Method validation summary	Acceptability
QC levels	Assay Negative Control (Heat inactivated pooled complement preserved normal human serum) Assay Positive Control (Pooled complement preserved normal human serum) TNT Control (100 µg/mL sutimlimab in pooled complement preserved normal human serum)	
Accuracy and precision	Intra-Assay and Inter-Assay Accuracy was met (36 out of 36 replicate pairs from all 6 runs) for all controls: OD of Assay negative control < 0.200 blOD of Assay positive control > 1.00 % Activity for TNT control >75%	Acceptable

	Intra-Assay Precision (%CV) was 4.1–6.4% for Assay positive control, 1.9–9.7% for Assay negative control, 5.5–7.9% for TNT control.	
	Inter-Assay Precision (%CV) was 4.9% for Assay positive control, 6.2% for Assay negative control, 6.4% for TNT control.	
Selectivity (normal/hemolyzed /lipemic/CAD)	No matrix interferences were observed in %AP activity regardless of the health status	
Interference & Specificity	This assay was found to be specific as it can differentiate sutimlimab from a similar human IgG4 at the same concentration level (100 µg/mL)	
Benchtop/ process stability	Up to 4 hours 27 minutes	
Freeze-Thaw stability	6 cycles at -60°C to -80°C and thawed on ice	
Refrigerator stability	Up to 24 hours 40 minutes	
Long term stability	Up to 12 months at -60°C to -80°C	

Reviewer's comments: Methods 1706 are semi-quantitative for measuring AP activity in complement preserved human serum. %AP activity was calculated as activity relative to a positive and negative control.

C1s

A complement component C1s LCMS/MS assay (Method LCMSD 954) was developed for quantitating total C1s (both sutimlimab bound C1s and non-sutimlimab bound C1s) in human plasma samples. This method was validated at (b) (4) and was used for Study 03.

Free C1s measurements were completed using exploratory research assays for all Phase 1 studies. However, the validation report for this exploratory research assay was not submitted.

Method LCMSD 954	
Analyte	C1s
Title	Quantitation of Total C1s (C1S) in Human Plasma via HPLC with MS/MS Detection
Method description	The procedure employed a hybrid HPLC with MS/MS detection method, samples were diluted, denatured, reduced, alkylated and digested to yield peptides specific for human C1s. The digested samples are purified with solid phase extraction plate. The final extract was separated via HPLC and detected via MS/MS detection using positive ion electrospray. Since the human tryptic peptides to be monitored are proteotypic in cynomolgus

	monkey plasma, cynomolgus monkey plasma was used as a surrogate matrix. Therefore, the validation was conducted using samples prepared in 2 types of matrix: human plasma (primary matrix) and cynomolgus monkey plasma (surrogate matrix).			
Internal Standard (IS)	(b) (4) -IS			
Primary Matrix	Human Plasma as primary matrix, and Cynomolgus Monkey Plasma as surrogate matrix			
Standard Curve Concentrations	2.00 to 100 µg/mL			
Surrogate Matrix QC Concentrations	2.00, 4.00, and 75.0 µg/mL			
Primary Matrix QC Concentrations	4.06, 42.2, and 71.1 µg/mL			
QC Intra-assay Statistics (%)	Concentration (µg/mL)	Precision	Accuracy	Acceptability
Surrogate Matrix	2 - 75	5.46% to 8.02%	-5.34 to -0.466%	Acceptable
Primary Matrix	4 - 71	2.03% to 6.69%	-4.24% to 2.99%	Acceptable
QC Inter-assay Statistics (%)				Acceptable
Surrogate Matrix	2 - 75	6.00% to 7.04%	-3.43% to -1.11%	Acceptable
Primary Matrix	4 - 71	4.31% to 5.76%	NA	Acceptable
Dilutional Linearity	71.1 µg/mL diluted 2-fold 192 µg/mL diluted 10-fold			
Freeze-thaw Stability (cycles)	Five cycles frozen at -80ºC and thawed on ice (surrogate matrix) Five cycles frozen at -25ºC or -80ºC and thawed on ice (primary matrix)			
Thawed Matrix Stability (hours)	4.2 hours on ice (surrogate matrix) 24 hours on ice and at room temperature (primary matrix)			
Extract Stability (hours)	89 hours at 2 to 8ºC			
Frozen Matrix Storage Stability (days)	7 days at -80ºC (surrogate matrix) 7 days at -25ºC and -80ºC (primary matrix)			
Whole Blood Stability	Two hours at room temperature and 2 hours in an ice bath prior to processing to plasma in a room temperature or refrigerated centrifuge			
C1s Stress Solution Stability (days)	1.01 mg/mL: 6.5 hour at room temperature in client provided solvent			
Hemolysis/Lipemia	No effect from hemolysis/lipemia on the quantitation of C1s			
Selectivity	No significant interfering peaks noted in blank human plasma samples			
Matrix Factor	Lot-to-lot response consistency was demonstrated for C1s			
Assay performance (Study 03)				

ISR	10.1% of the study samples were reassayed. Acceptance rate with a 94.1% pass rate.	Acceptable
Calibration standard concentrations	2.00, 3.20, 4.80, 10.0, 20.0, 50.0, 80.0, and 100 µg/mL	
Precision and accuracy for calibration curve	Precision (%CV): <5.66% Accuracy (%bias): -1.69% to 1.08%	Acceptable
Primary QC concentrations	4.06, 42.2, and 71.1 µg/mL, prepared 18 Jun 2019 3.53, 36.3, and 65.5 µg/mL, prepared 10 July 2019	
Precision and accuracy for QC	Precision (%CV): <10.1% Accuracy (%bias): -2.51% to 12.8%	Acceptable

Reviewer's comment: Method LCMSD 954 was adequate to support the total C1s analysis for samples from Study 03. Since the validation report for exploratory research assays for free C1s analysis was not submitted, we could not further verify the acceptability of this method. However, this has no major impact on our review or drug label.

C4

Commercially available immunoturbidity assay kits were used for quantitative measurement of complement component 4 (C4) samples from studies 01 Parts (A-C), 02, 05, and 03. The analysis was performed at (b) (4) a CLIA lab. The C4 assays measure increasing sample turbidity caused by the formation of insoluble immune complexes when antibody to C4 is added to the sample. The complement C4 was part of an FDA-cleared chemistry panel and was run on Siemens ADVIA 1800 chemistry system. The chemistry panel, ADVIA® Chemistry Liquid Specific Protein Calibrators, which includes Complement C4, was cleared as an *in vitro diagnostics* (IVD) by FDA for *in vitro* diagnostic use (510(K) Number: K103701).

(b) (4) has performed CLIA-level method validation and the accuracy and precision are acceptable, with the calibration curve ranged from 0.4 to 150 mg/dl.

Reviewer's comment: The analytical method for C4 is acceptable.

Immunogenicity

Please refer to OBP review by Dr. Xiaoshi Wang for detailed information regarding bioanalytical methods measuring ADAs for sutimlimab in serum.

4.2 Pharmacometrics Review

Applicant's Reports Reviewed by Pharmacometrics Reviewer

Report No.	Note
Study-pho0755	Population PK analysis
Study-pho0757-ER analysis	Exposure-Response Analysis

4.2.1. Population PK Analysis

Applicant's Population PK analysis

The Applicant conducted the population PK (PPK) analyses based on data from 4 clinical studies (**Table 4**), to describe PK of sutimlimab in patients with primary CAD and explore demographic and laboratory covariates that may affect the PK of sutimlimab in patients with primary CAD. Baseline patient characteristics for PPK dataset are summarized in **Table 5**. Studies TNT009-01, TNT009-02 and BIVV009-05 are complete and Study BIVV009-01 has completed Part A and Part B is ongoing at the time of PPK analysis.

Table 4. Studies included in PPK analysis

Study Design	Sutimlimab Dosing[a]
TNT009-01 Phase 1, placebo-controlled, single- and multiple-ascending dose study to assess the safety, tolerability, and activity of TNT009 in healthy subjects and patients with complement-mediated disorders	Part A: Single dose of 0.3 mg/kg ascending through 100 mg/kg. Part B: Weekly dosing of 30 or 60 mg/kg for 4 weeks. Part C: Test dose (10 mg/kg) and subsequent weekly dosing at 60 mg/kg for 4 weeks. Part E: Day 0, Week 1, and every 2 weeks thereafter until the last visit at which the study drug is administered (5.5 g per dose); when evidence of biochemical breakthrough hemolysis is observed, re-loading with an additional dose of 5.5 g is permitted. Also, re-loading is permitted before and/or after prolonged vacation (>16 days).
TNT009-02 Phase 1, placebo-controlled, dose confirmation study to assess the safety, tolerability, PK, and PD of multiple-dose TNT009 in healthy subjects	75 mg/kg on Days 1, 8, 22, and 36.

BIVV009-03 (CARDINAL) Phase 3, open-label, single-arm, multicenter study in patients with primary CAD who have a recent history of blood transfusion	Patients < 75 kg: fixed dose of 6.5 g. Patients ≥ 75 kg: fixed dose of 7.5 g. Part A: Dose administered on Day 0, Day 7, and every 14 days thereafter through Week 25 Part B: Same as in Part A.
BIVV009-05 Phase 1 study to assess the safety, tolerability, PK, and PD of single-dose and multiple-dose BIVV009 in healthy Japanese subjects	Part A: Single dose of 30 mg/kg (Cohort 1), 60 mg/kg (Cohort 2), and 100 mg/kg (Cohort 3). Part B: Fixed dose of 6.5 g on Days 1, 8, and 22 in healthy subjects < 75 kg (Cohort 4) and fixed dose of 7.5 g on Days 1, 8, and, 22 in healthy subjects ≥ 75 kg (Cohort 5).
[a] The route of administration in all studies was intravenous infusion.	

Source: Applicant's PPK report. Table 1, page 12.

Table 5. Summary of Baseline Covariates of PK Analysis Subjects

Covariate Statistic/Category	TNT009-01 (n=82)	TNT009-02 (n=18)	BIVV009-03 (n=24)	BIVV009-05 (n=30)	Overall (n=154)
Sex					
Female	41 (50.0%)	1 (5.6%)	15 (62.5%)	5 (16.7%)	62 (40.3%)
Male	41 (50.0%)	17 (94.4%)	9 (37.5%)	25 (83.3%)	92 (59.7%)
Race					
Caucasian	78 (95.1%)	9 (50.0%)	3 (12.5%)	0 (0%)	90 (58.4%)
Asian	1 (1.2%)	1 (5.6%)	3 (12.5%)	30 (100%)	35 (22.7%)
Black or African American	2 (2.4%)	8 (44.4%)	0 (0%)	0 (0%)	10 (6.5%)
Other	1 (1.2%)	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)
Missing	0 (0%)	0 (0%)	18 (75.0%)	0 (0%)	18 (11.7%)
Ethnicity					
Non-Japanese	82 (100%)	18 (100%)	21 (87.5%)	0 (0%)	121 (78.6%)
Japanese	0 (0%)	0 (0%)	3 (12.5%)	30 (100%)	33 (21.4%)
Disease status					
Healthy subject	48 (58.5%)	18 (100%)	0 (0%)	30 (100%)	96 (62.3%)
Cold agglutinin disease	10 (12.2%)	0 (0%)	24 (100%)	0 (0%)	34 (22.1%)
Bullous pemphigoid	10 (12.2%)	0 (0%)	0 (0%)	0 (0%)	10 (6.5%)
antibody-mediated rejection	10 (12.2%)	0 (0%)	0 (0%)	0 (0%)	10 (6.5%)
warm autoimmune hemolytic anemia	4 (4.9%)	0 (0%)	0 (0%)	0 (0%)	4 (2.6%)
Anti-Drug Antibody Positive					
No	76 (92.7%)	17 (94.4%)	0 (0%)	27 (90.0%)	120 (77.9%)
Yes	6 (7.3%)	1 (5.6%)	0 (0%)	3 (10.0%)	10 (6.5%)
Missing	0 (0%)	0 (0%)	24 (100%)	0 (0%)	24 (15.6%)
Age (years)					
Mean (SD)	45.5 (19.7)	33.3 (8.42)	71.3 (8.18)	41.8 (9.01)	47.4 (19.0)
Median [Min, Max]	39.5 [19.0, 88.0]	33.5 [21.0, 46.0]	71.5 [55.0, 85.0]	41.0 [26.0, 56.0]	43.5 [19.0, 88.0]

Covariate Statistic/Category	TNT009-01 (n=82)	TNT009-02 (n=18)	BIVV009-03 (n=24)	BIVV009-05 (n=30)	Overall (n=154)
Body weight (kg)					
Mean (SD)	73.3 (13.1)	80.7 (15.9)	67.8 (15.8)	68.6 (13.3)	72.4 (14.3)
Median [Min, Max]	72.5 [48.0, 98.0]	79.4 [45.6, 109]	66.5 [40.2, 112]	66.9 [44.0, 102]	71.9 [40.2, 112]
Albumin (g/L)					
Mean (SD)	NA (NA)	45.9 (4.71)	40.9 (3.05)	47.3 (2.39)	44.8 (4.34)
Median [Min, Max]	NA [NA, NA]	46.0 [39.0, 55.0]	41.0 [34.0, 48.0]	47.0 [43.0, 53.0]	45.0 [34.0, 55.0]
Missing	82 (100%)	0 (0%)	0 (0%)	0 (0%)	82 (53.2%)
ALT (U/L)					
Mean (SD)	19.7 (8.16)	24.8 (8.30)	30.0 (28.0)	32.9 (18.3)	24.5 (16.0)
Median [Min, Max]	18.0 [7.00, 45.0]	26.0 [14.0, 40.0]	19.0 [11.0, 142]	28.5 [14.0, 90.0]	20.0 [7.00, 142]
AST (U/L)					
Mean (SD)	22.6 (7.67)	22.3 (4.50)	37.7 (18.8)	27.1 (8.37)	25.8 (11.4)
Median [Min, Max]	20.0 [10.0, 54.0]	21.0 [14.0, 34.0]	34.0 [15.0, 83.0]	24.5 [18.0, 53.0]	23.0 [10.0, 83.0]
Bilirubin (mg/dL)					
Mean (SD)	0.906 (1.39)	0.789 (0.270)	2.98 (1.37)	0.803 (0.257)	1.20 (1.39)
Median [Min, Max]	0.480 [0.110, 9.20]	0.800 [0.400, 1.50]	2.68 [0.940, 6.57]	0.800 [0.400, 1.50]	0.700 [0.110, 9.20]
CRCL (mL/min)					
Mean (SD)	99.4 (37.7)	124 (24.3)	71.7 (33.2)	122 (22.1)	102 (36.8)
Median [Min, Max]	101 [30.6, 173]	124 [67.7, 173]	62.8 [23.8, 174]	117 [89.2, 178]	106 [23.8, 178]
EGFR (mL/min/1.73 m^2)					
Mean (SD)	88.4 (31.7)	105 (18.9)	82.4 (29.2)	119 (19.1)	95.3 (30.7)
Median [Min, Max]	92.6 [23.2, 178]	102 [72.1, 160]	77.1 [26.9, 133]	113 [90.3, 159]	99.8 [23.2, 178]

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; CRCL=creatinine clearance; EGFR=estimated glomerular filtration rate; Max=maximum; Min=minimum; n=number of subjects; PK=pharmacokinetic; SD=standard deviation.

Source: Applicant's PPK report, Table 5, page 24.

The final population PK model for sutimlimab following IV administration is a 2-compartment disposition model with parallel linear and non-linear clearance terms. Between-subject variability (BSV) terms are included on CL, volume of distribution of the central compartment (Vc), volume of distribution of the peripheral compartment (Vp), and maximum non-linear clearance (Vmax). The residual error model includes additive and proportional error terms for CARDINAL (BIVV009-03) and separate additive and proportional error terms for other studies. The post-dose BLQ samples made up 7.6% of all post-dose PK observations and the BLQ samples were set to missing for the final model. Final model parameter estimates are presented in **Table 6** and the standard goodness of fit plots are presented in **Figure 4**.

Table 6. Parameter Estimates of Final PPK Model

	Estimate		Interindividual Variability		
Parameter (unit)	**Typical Value**	**RSE[a]**	**Typical Value**	**RSE[a]**	**Shrinkage[b]**
Clearance (CL, mL/hr)	5.65	7.6%	34%	16%	35%
Effect of body weight on CL[c]	1.72	11%	—	—	—
Intercompartmental clearance (Q, mL/hr)	19.7	7.1%	—	—	—
Central volume of distribution (Vc, mL)	3841	2.2%	21%	5.4%	25%
Effect of body weight on Vc[c]	0.52	18%	—	—	—
Japanese ethnicity effect on Vc	-29%	9.8%	—	—	—
Peripheral volume of distribution (Vp, mL)	1994	4.5%	55%	19%	5.2%
Maximal non-linear clearance (Vmax, µg/hr)	9870	4.0%	20%	15%	23%
Japanese ethnicity effect on Vmax	-30%	21%	—	—	—
BIVV009 concentration required for half-maximal non-linear clearance (Km, µg/mL)	8.7	29%	—	—	—
Residual variability					
CARDINAL study proportional residual error	27%	10%	—	—	3.9%
CARDINAL study additive residual error SD (µg/mL)	111	21%	—	—	3.9%
Non-CARDINAL studies proportional residual error	14%	4.4%	—	—	8.7%
Non-CARDINAL studies additive residual error SD (µg/mL)	5.7	8.1%	—	—	8.7%

Abbreviations: %CV=percent coefficient of variation, BSV=between-subject variability; RSE=relative standard error, SD=standard deviation; SE=standard error; — =not determined.

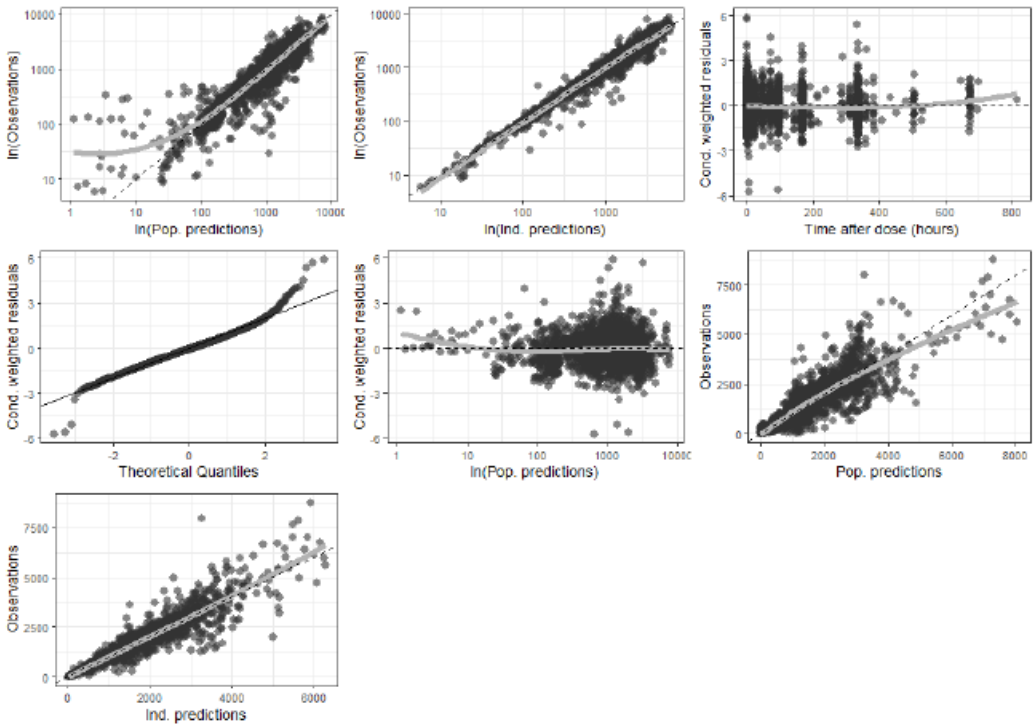
[a] RSE of parameter estimate are calculated as 100 × (SE/typical value); RSE of BSV magnitude are presented on %CV scale and approximated as 100 × (SE/variance estimate)/2.

[b] Shrinkage (%) is calculated as 100 × (1 – SD of post hocs/estimated variance).

[c] Effect of body weight is relative to the median body weight of 71.85 kg.

Source: Applicant's PPK report, Table 8, page 33.

Figure 4. Goodness of Fit Plot of Final PPK model



Abbreviations: Cond.=conditional; Ind.=individual; ln=natural logarithm; PK=pharmacokinetic; Pop.=population.
Note: The circles represent individual data points, the grey lines represent loess smooth curves, and the dashed and solid lines represent either the line of unity (y=x) or the x-axis (y=0).

Source: Applicant's PPK report, Figure 9, page 35.

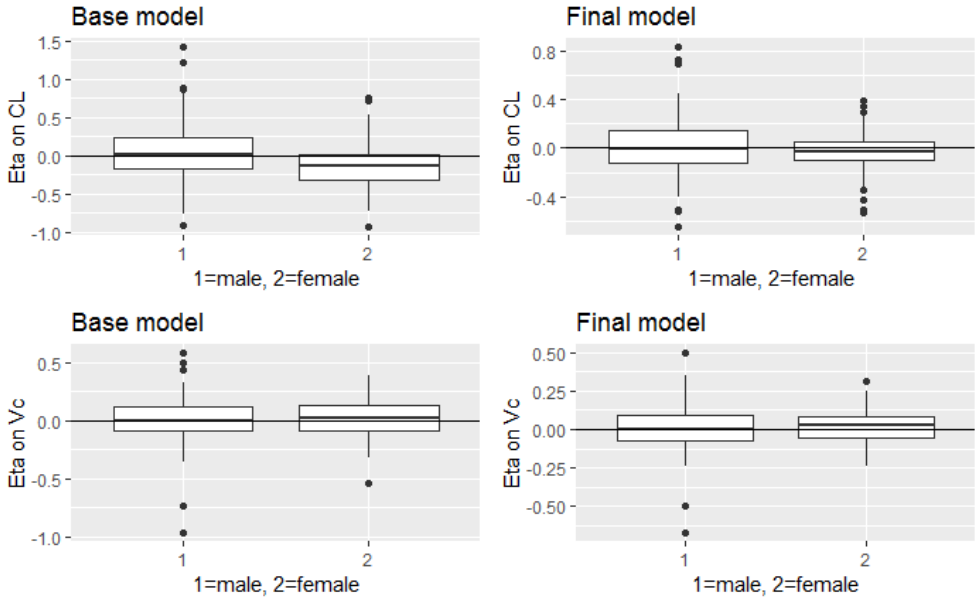
Body weight and ethnicity (Japanese, non-Japanese) were identified as covariates impacting sutimlimab PK. Body weight when normalized to the median value of 71.85 kg, showed a greater than proportional change in CL (power of 1.72) and a less than proportional change in Vc (power of 0.52). At the proposed dosing regimen, the steady-state exposures are estimated to range from 47% to 157% for the 5th (58 kg) and 95th (98 kg) percentiles of body weight relative to the median body weight of 71.85 kg. Japanese subjects had lower Vc and Vmax, by 29% and 30% respectively, compared to non-Japanese subjects. Japanese subjects had a greater exposure 23% to 33% compared to non-Japanese subjects. Sex, race, disease status, age, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, creatinine clearance, estimated glomerular filtration rate (eGFR), and presence or absence of anti-drug antibodies (ADAs) were tested, but after including the covariates listed above did not have an additional impact on sutimlimab PK.

Reviewer's Assessment of PPK analysis

The applicant's PPK model adequately describes the observed concentrations observed across different studies included in PPK analysis:

- Parameter estimates for the final model were estimated with acceptable precision with relative standard error (RSE) and the shrinkage for IIV on CL (35%) and Vc (25%) were acceptable. The final model did not show obvious bias over time on predicted concentrations. The prediction-corrected visual predictive checks (pcVPCs) demonstrated an agreement between the observed and the simulated concentrations (Applicant's report. Figure 10 on page 36).
- The applicant's covariate models are adequate as the relationships between ETAs and the covariates (body weight, and ethnicity) for final model were improved without showing an obvious trend (Applicant's report Figure 20-22 on pages 73-78) after incorporating the respective covariates.
- Though the PPK analysis did not identify sex as an influential covariate for sutimlimab PK, a notable difference in exposure between female and male patients is observed in CARDINAL (See Section 3.3.3). In the examination of ETA-covariate relationships (Figure 5), the ETAs were centered around zero without a notable bias for males and females in the final PPK model where body weight and ethnicity were incorporated (Figure 5, top right). The reviewer opines that the PK difference in sex observed in CARDINAL is likely due to the body weight/ethnicity distributions rather than intrinsic sex effect on PK.

Figure 5. ETAs for CL and Vc - Sex relationships for the base model (left) and the final model (right)



Source: Reviewer's figure.

- Body weight effect was incorporated by allometric scaling with estimated exponent of 1.72 which lead to great variability in exposure across the body weight range. The body weight normalized exposures are expected to vary from 157% to 41% for the body weight of 50.5 kg (5^{th} percentile) and 98 kg (95^{th} percentiles) relative to the median body weight of 71.9 kg. The proposed two-tier weight-based dose regimen provides a little improvement (157% to 47%) on the exposure variability.

- The applicant's PPK analysis showed that linear clearance was not significantly different across varying degrees of renal function (23.2-178 mL/min/1.73 m^2 estimated by eGFR). As only 3 patients in PPK datasets had severe renal impairment (eGFR <30 mL/min/1.73 m^2), any inference cannot be made on the influence of severe renal function on sutimlimab PK.
- Due to the different ADA assays used in the trials included in the PPK analysis and the limited data of the reported ADA, the impact of ADA on PK was not evaluated further by Pharmacometrics reviewer (Refer to Section 3.3.3. Immunogenicity).

1. Exposure-Response Analysis

Applicant's Exposure-Response (E-R) Analysis

The applicant's E-R analysis for hemoglobin response were performed based on the data from a total of 34 patients who had primary CAD (CARDINAL (n=24) and BIVV009-01 Part C (n=9)). The graphical examination shows that the maximum change in Hgb was similar across the range of simulated steady-state sutimlimab C_{min} in CAD patients. In the analysis of time-matched observed Hgb increase and observed sutimlimab concentrations where Emax model was fitted (**Table 7**), the model estimated E_{max} was 2.7 g/dL and the EC_{50} was 192 µg/mL. The model-estimated E_{max} was greater than the 2 g/dL increase in Hgb specified in the protocol in the primary efficacy endpoint. The steady-state C_{min} values for all 24 patients in CARDINAL were greater than the EC_{50} of 192 µg/mL.

Table 7. Parameters of the Time-Matched Observed Hgb versus Observed BIVV009 Concentration Model

	Estimate		Interindividual Variability		
Parameter (unit)	**Typical Value**	**RSE[a]**	**Typical Value**	**RSE[a]**	**Shrinkage[b]**
Baseline Hgb (Hgb_0, g/dL)	8.3	3.2%	16%	20%	12%
Maximum Hgb change (E_{max}, g/dL)	2.7	15%	51%	22%	19%
BIVV009 Concentration for 50% of E_{max} (EC_{50}, µg/mL)	192	34%	—	—	—
Residual variability					
Additive residual error SD (g/dL)	1.0	8.0%	—	—	5.4%

Abbreviations: %CV=percent coefficient of variation; BSV=between-subject variability; EC_{50}=BIVV009 concentration required to achieve 50% of maximal effect; E_{max}=maximal effect; Hgb=hemoglobin; Hgb_0=baseline hemoglobin; PK=pharmacokinetic; RSE=relative standard error; SD=standard deviation.
[a] RSE of parameter estimate are calculated as 100 × (SE/typical value); RSE of BSV magnitude are presented on %CV scale and approximated as 100 × (SE/variance estimate)/2.
[b] Shrinkage (%) is calculated as 100 × (1 – standard deviation of post hocs/estimated variance).

Source: Applicant's E-R report, Table 6, page 31.

The Applicant further explored the longitudinal model for Hgb assuming that steady-state sutimlimab C_{min} have saturated the exposure-based response (sutimlimab exposure was not included in the model). The longitudinal model for Hgb had an E_{max} of 4.3 g/dL in females and 1.6 g/dL in males and a typical time to 50% of maximal effect (t_{50}) of 7.4 days, which suggests that maximal Hgb level is achieved in less than 40 days (assuming 5 half-lives to achieve steady-state). The predicted increase in Hgb, independent of sex effects, was 2.7 g/dL (time-matched model) and 3.3 g/dL (longitudinal model), both of which are greater than the target Hgb increase of 2 g/dL for clinical benefit for patients with CAD.

Table 8. Parameter Estimates of the Final Longitudinal Model for Hgb

	Estimate		Interindividual Variability		
Parameter (unit)	**Typical Value**	**RSE [a]**	**Typical Value**	**RSE[a]**	**Shrinkage[b]**
Baseline Hgb (Hgb_0, g/dL)	8.3	2.6%	10%	17%	12%
Effect of baseline CRCL[c] on Hgb_0	0.22	25%	—	—	—
Maximum Hgb change for female (E_{max}, g/dL)	4.3	9.3%	22%	34%	36%
Male effect on E_{max}	-63%	12%	—	—	—
Effect of predose Hgb[d] on E_{max}	-2.3	34%	—	—	—
Time to 50% of E_{max} (t_{50}, days)	7.4	25%	62%	25%	45%
Effect of predose Hgb[d] on t_{50}	-9.5	20%	—	—	—
Residual variability					
Additive residual error SD (g/dL)	0.85	9.4%	—	—	3.7%

Abbreviations: %CV=coefficient of variation; BSV=between-subject variability; E_{max}=maximal effect; Hgb=hemoglobin; Hgb_0=baseline hemoglobin; RSE=relative standard error; SD=standard deviation; SE=standard error; t_{50}=time required to achieve 50% of maximal effect.

[a] RSE of parameter estimate are calculated as 100 × (SE/typical value); RSE of BSV magnitude are presented on %CV scale and approximated as 100 × (SE/variance estimate)/2.

[b] Shrinkage (%) is calculated as 100 × (1 – SD of post hocs/estimated variance).

[c] Effect of baseline CRCL is relative to the median of 66 mL/min.

[d] Effect of predose Hgb is relative to the median of 8.4 g/dL.

Source: Applicant's E-R report, Table 10, page 40.

The Applicant concluded that the observed data also suggests that the Hgb response is saturated at the dosing regimen used in CARDINAL, hence the proposed dosing regimen provides adequate sutimlimab exposure at steady state to maximize the effect on Hgb. Because of the paucity of adverse event data, the Applicant did not conduct exposure-safety analysis.

Reviewer's Assessment of E-R analysis for Efficacy

Overall, the reviewer agrees with the applicant's conclusions. Due to hysteresis between hemoglobin change and sutimlimab concentrations (reported by the applicant), the time-matched E-R analysis may not likely fully capture the E-R relationship for hemoglobin response. The reviewer's independent analysis and assessment for E-R relationship are provided in Sections 3.3 Clinical Pharmacology Questions. Following are the additional assessments:

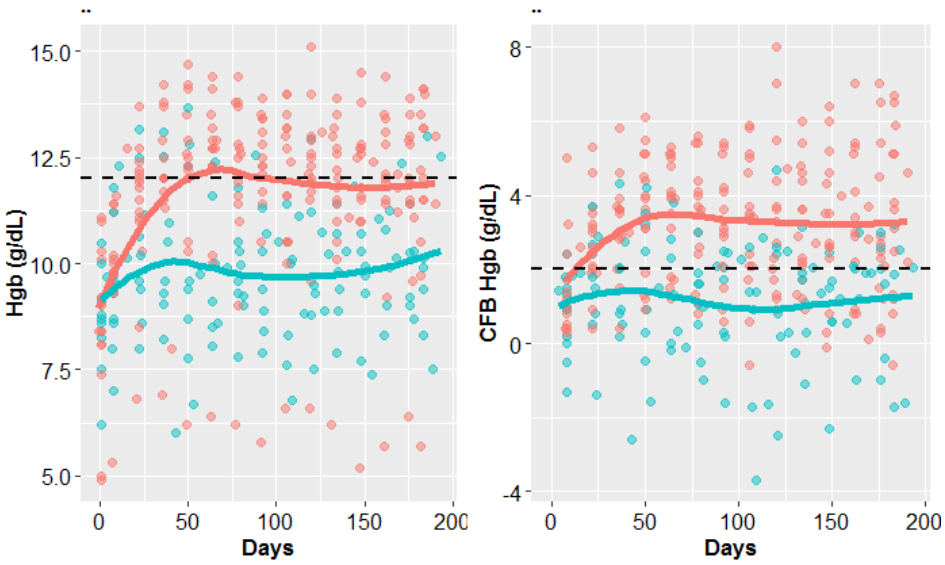
E-R relationship for efficacy:

The reviewer performed univariate logistic regressions to further confirm the E-R relationship for hemoglobin response and composite response with the exposure metrics (steady-state AUC and C_{min}) and no statistically-significant relationship was noted. Note that two patients who met the hemoglobin criteria at TAT, failed to meet the criteria for primary efficacy endpoint requiring blood transfusions after Week 5. Both patients had 1 or more occasions where the dosing interval exceeded 17 days. Based on the data from two patients, any inference cannot be made whether the requirement for transfusions in these patients was due to the temporarily lower exposure because of delayed dose interval (i.e., > 17 days) or other patient characteristics (i.e., baseline disease states).

Sex difference in hemoglobin response:

Due to the small sample size (9 males and 15 females), E-R relationships grouped by sex could not be conducted. However, the magnitude of hemoglobin response was in general greater in female patients compared to male patients, as shown in the time-course of hemoglobin grouped by sex (Figure 6). Male patients experienced smaller changes from baseline and lower absolute values in hemoglobin levels throughout the study. A similar trend was observed in the E-R analysis for hemoglobin response at TAT.

Figure 6. Time course of Hemoglobin Response Grouped by Sex in CAD patients from CARDINAL



Source: Reviewer's figure. Red/blue dots represent female and male patients, respectively. Red/blue lines represent loess smoothers for female and male patients, respectively. Dashed lines represent the absolute hemoglobin level of 12 g/dL (bottom panel), and the hemoglobin level change from baseline by 2 g/dL (left panel)

In the PPK analysis conducted based on four studies (TNT009-01, TNT009-02, CARDINAL, and BIVV009-05), sex was not a significant covariate for sutimlimab PK. However, in CARDINAL, a lower sutimlimab exposure in male patients was observed compared to female patients (Figure 3). The sex-difference in exposure is partially explained by different body weight distribution between female and male patients enrolled in CARDINAL. Mean of body weights were 64.8 kg vs 72.8 kg for female and male patients, respectively. Despite the observed lower exposure compared to those of female patients, C_{min} levels in male patients were above the PK threshold (100 µg/mL). Furthermore, no clear E-R relationship was observed in the observed C_{min} range in all subjects (female and male patients). There is no sufficient data to conclude that the difference in efficacy between female and male patients is due to the PK difference. Therefore, a dose increase in male patients is not likely to improve hemoglobin response.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

XIAOLEI N PAN
11/06/2020 04:17:00 PM

JIHYE AHN
11/06/2020 04:18:26 PM

JUSTIN C EARP
11/06/2020 04:25:51 PM

SUDHARSHAN HARIHARAN
11/06/2020 04:29:23 PM

SHIRLEY K SEO
11/06/2020 04:35:33 PM